wherein the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is present in a complex with the linoleic acid component, the complex substantially remains intact in an aqueous environment.

REMARKS

The above-identified application has been carefully reviewed in light of the Office Action mailed December 17, 2001. Enclosed is a Request for Extension of Time, and required fee, extending the period for responding to the Office Action to and including April 17, 2002.

Claims 1 and 23 have been rewritten to make more clear that which was intended in the original claims. Specifically, claims 1 and 23 have been rewritten to make clear that a complex is present in the present compositions. These amendments are fully supported by the above-identified application, as originally filed. Moreover, the rewritten claims 1 and 23 are not more narrow in scope than claims 1 and 23 as originally filed. Therefore, applicant submits that the new claims are allowable and that the rule in the Festo case does not apply in the current circumstance.

Claims 1 to 23 have been rejected under 35 U.S.C. 103 as being unpatentable over Cupps et al. Applicant traverses this rejection.

The present invention is directed to compositions comprising an alpha-2-adrenergic agonist, and a fatty acid component in which the fatty acid component is present in a complex with the alpha-2-adrenergic agonist. The complex, for example an ion pair complex, remains substantially intact in an aqueous environment, that is, the complex remains substantially as a single, stiochiometric entity in an aqueous environment.

In independent claim 23, compositions are provided comprising 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline and a linoleic acid component wherein the quinoxaline is present in a complex with the linolenic acid component and the complex remains substantially intact in an aqueous environment.

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The present compositions comprising the complexes as noted above provide surprising and substantial benefits. For example, the presence of the fatty acid component in the complex preferably is effective to enhance the efficacy of the complexed agonist relative to the efficacy of the uncomplexed agonist, that is the agonist not complexed with the fatty acid component. The agonist-fatty acid component complex preferably is such that the fatty acid component is present in an amount effective to enhance the movement of the agonist across a lipid membrane, or across a biological membrane under physiological conditions.

Applicant has presented data illustrating the surprising and important benefits of the present compositions comprising alpha-2-adrenergic agonist-fatty acid component complexes. Submitted herewith are pages 19 to 23 of the present specification which set forth Example 2.

In this Example 2, three compositions were tested to determine relative sedative effects. These compositions were as follows: bromonidine-linoleic acid complex (65), an embodiment of the present invention; saline (62); and bromonidine tartrate (60).

Each of these compositions was introduced into the eyes of monkeys as described in Example 2. The ability of a composition to be introduced into an eye, for example, to reduce intraocular pressure, without causing the side effect of sedation is an advantageous property. That is to say, reduced sedation is a substantial beneficial result in the tests of Example 2.

As shown in Example 2, dosing with the present bromonidine-linoleic acid complex (65) causes more sedation in the monkeys than does dosing with saline (62). Importantly, however, dosing with bromonidine tartrate (60) causes more sedation than dosing with the complex. Thus, the bromonidine-linoleic acid complex advantageously reduces sedation side effects relative to uncomplexed bromonidine, that is bromonidine tartrate (60). This is an important benefit of the present invention in that both the bromonidine-linoleic acid complex and the bromonidine tartrate are

effective, when administered to an eye, to reduce the intraocular pressure in the eye. However, the present bromonidine-linoleic acid complex surprisingly has reduced sedative side effects relative to the bromonidine tartrate. Providing a composition which has reduced side effects is highly advantageous.

Cupps et al discloses the use of certain compounds for preventing or treating of disorders modulated by alpha-2-adrenoceptors. At column 14 lines, 53 to column 15 line 2, (relied on in part by the Examiner), Cupps et al discloses examples of substances as pharmaceutically-acceptable carriers or components thereof including sugars; starches; cellulose and its derivatives; powdered tragacanth; malt; gelatine; talc; solid lubricants; calcium sulfate; vegetable oils; polyols; alginic acid; emulsifiers; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

Cupps et al does not disclose, teach or suggest the present invention. For example, Cupps et al does not disclose, teach or even suggest any complexes, let alone alpha-2-adrenergic agonist-fatty acid component complexes, as recited in the present claims. In addition, Cupps et al does not even suggest the surprising and substantial benefits of the present compositions comprising alpha-2-adrenergic agonist-fatty acid component complexes set forth in the above-identified application, for example, as demonstrated in Example 2 of the above-identified application.

The large group of possible carriers or components thereof disclosed by Cupps et al, described above, make abundantly clear that Cupps et al does not even suggest, contemplate or recognize alpha-2-adrenergic agonist-fatty acid component complexes, as recited in the present claims. For example, there is nothing in the disclosure of Cupps et al which provides any motivation or incentive whatsoever to one of ordinary skill in the art to pick and choose from among the many carriers and components thereof described in Cupps et al to select materials that even could

provide the present complexes. Moreover, Cupps et al provides not the slightest suggestion that such complexes even exist, let alone that such complexes provide the surprising and substantial advantages achieved by applicant.

Cupps et al discloses stearic acid and magnesium stearate as solid lubricants. Further, Cupps et al discloses a genus of oils which may be combined with an adrenergic agonist. This disclosed genus of oils includes fatty acids, non-fatty acids and other oils.

Again, one of ordinary skill in the art is provided with no motivation or incentive from Cupps et al to pick and choose from among the large group of materials disclosed by Cupps et al as carriers or components thereof to select fatty acid components and produce compositions comprising alpha-2-adrenergic agonist-fatty acid component complexes as recited in the present claims, let alone to do so and obtain the surprising and substantial benefits achieved by applicant.

Applicant, and applicant alone, has discovered that compositions comprising alpha-2-adrenergic agonist-fatty acid component complexes which remain substantially intact in an aqueous environment can be formed and provide the substantial benefits, for example, reduced sedative side effects, obtained by applicant. Cupps et al does not disclose or even suggest any complexes, let alone the alpha-2-adrenergic agonist-fatty acid component complexes recited in the present claims.

The Examiner contends that one skilled in the art would have been motivated to employ the teachings of Cupps et al since Cupps et al relates to the use of alpha 2 adrenergic agonists in combination with fatty acids in a pharmaceutical formulation. Applicant vigorously disagrees.

As noted above, Cupps et al discloses a very large catalog of materials for inclusion with alpha 2 adrenergic agonists in pharmaceutical compositions. Nothing in the disclosure of Cupps et al would lead one of ordinary skill in the art to choose fatty acids over the large number of other materials disclosed in the

same paragraph of Cupps et al, as described above. Moreover, even if fatty acids are chosen, there is no suggestion whatsoever in Cupps et al that fatty acids and the alpha-2-adrenergic agonists should be used to form complexes which remain substantially intact in an aqueous environment, as recited in the present claims and which provide surprising and substantial benefits, for example, reduced sedative side effects, as demonstrated in the above-identified application.

Put another way, only after knowing of applicant's invention and disclosure would one or ordinary skill in the art pick and choose from among the carriers and components thereof disclosed by Cupps et al and select a fatty acid and then combine the fatty acid with an alpha-2-adrenergic agonist in such a way to form a complex, for example, an ion pair complex, and then obtain the surprising and substantial benefits achieved by applicant. In short, the very broad disclosure of Cupps et al can be mechanically manipulated only with hindsight knowledge gleaned only from the above-identified application to arrive at the present compositions recited in the present claims and the surprising and substantial benefits achieved by applicant. Such hindsight reconstruction and extension of the prior art is an improper basis for rejecting patent claims.

The Examiner questions the presence of a complex, contending that a mixture of different compounds always creates some kind of complex. Applicant disagrees.

The Examiner's statement that a mixture of different compounds always creates some kind of complex is not understood. Many mixtures of compounds can be produced without providing any kind of complex, as that term is used in the above-identified application. The present complexes are clearly one or more specific species. For example, the complex is identified as being substantially intact in an aqueous environment. Moreover, applicant has demonstrated that an embodiment of the present complexes provides reduced sedative effects, relative to the use of an uncomplexed

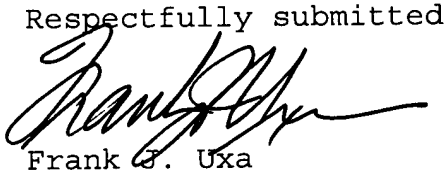
alpha-2-adrenergic agonist. Clearly, applicant has presented evidence to establish the unexpected and unobvious nature of the claimed invention. Cupps et al does not disclose, teach or even suggest the alpha-2-adrenergic agonist-fatty acid component complexes recited in the present claims.

In view of the above, applicant submits that claims 1 to 23 are unobvious from and patentable over Cupps et al under 35 U.S.C. 103.

Each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach or even suggest the present compositions including the additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

In conclusion, applicant has shown that claims 1 to 23 are unobvious from and patentable over the prior art under 35 U.S.C. 103. Therefore, applicant submits that the present claims are allowable and respectfully requests that Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,



Frank G. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (494) 450-1764

ATTACHMENT: VERSION WITH MARKINGS TO SHOW CHANGES MADE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A composition comprising:

an alpha-2-adrenergic agonist, and

a fatty acid component, the fatty acid component [forms] being present in a complex with the alpha-2-adrenergic agonist; the complex remaining substantially intact in an aqueous environment.

23. (Amended) A composition comprising:

[a] 5-bromo-6-(2-imidozolin-2-ylamino) [quinoxa-line] quinoxaline; and

a linolenic acid component,

wherein the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline [forms] is present in a complex with the linoleic acid component, the complex substantially remains intact in an aqueous environment.

of Intra Ocular Pressure (mm Hg) after an administration of bromonidine-linoleic acid complex at time 0. The complex is an ion pair formulation of 0.131% bromonidine and 0.126% linoleic acid.

0 hr	administration of complex
1 hr	-10.4%
2 hr	-16.0%
4 hr	-09.5%
6 hr	-09.4%

EXAMPLE 2

Relative sedative effects of various compounds

The relative sedative effects of bromonidine-linoleic acid (compound 65) were compared to saline (compound 62) and Brimonidine tartrate (compound 60). This study involved cross overs and a one-week wash out in between the administration of the various compounds.

As done in a previous experiment, the following method was followed:

1. 6 trained monkeys were placed in chairs and allowed to acclimate for approximately 30 minutes.
2. Individual monkeys were brought into the "testing room" where they were allowed to adjust to the new environment for approximately 2 minutes. After this adjustment time the monkey was observed for 1-2 minutes after which a sedation score was given. Sedation scores were recorded on an observation sheet.
3. The monkey was returned to the group of animals assigned to this study.
4. 2 baseline readings were done at T-0.5 and 0

hour. After the 0 hour reading one drop of the test compound was administered to the right eye.

5. Steps 2 & 3 were repeated at T=0.5, 1, 2, 3 and 4 hour.
6. Animals were monitored until they recover from effects of the drug.
7. Scoring of Sedation was based on the following scale:
   - S=0 Monkey is quiet, but slightly active.
   - S=1 Monkey is quiet, easy to handle for reading
   - S=2 Monkey is quiet, relaxed but very low in activity
   - S=3 Monkey is blinking eyes and yawning
   - S=4 Monkey is sleepy and inactive, eyes are heavy
8. The test compounds were coded: 62-Saline, 65-bromonidine tartrate, 60-bromonidine-linoleic acid.
9. Test Compound Administration:

animal #1	week 1	week 2	week 3
19	62	65	60
24	62	65	60
42	65	60	62
50	65	60	62
57	60	62	65
58	60	62	65

The scoring was conducted for each animal for the different test compounds. The average results are shown on table 1.

Table 1

Comparison of the sedative effects of Brimonidine-Linoleic Acid ion pair complex (0.2%) to Brimonidine Tartrate (0.2%) and saline.

Brimonidine-Linoleic Acid Ion Pair Complex

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	1.0
0.5	1.2
1	1.5
2	1.8
3	1.6
4	1.6

Brimonidine Tartrate

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	0.8
0.5	0.8
1	1.7
2	2.6
3	2.5
4	2.7

Saline Vehicle

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	1.0
0.5	1.0
1	1.0
2	1.2
3	1.3
4	1.3

The first reading after dosing, 0.5 hr-time point, the monkeys were quiet and easy to handle. In general, the animals started to show low activity when brought into the test room at the 1hr time.

Half the monkeys given the test compound bromonidine-linoleic showed low activity (1 hour post dose), with the exception of monkey #19. Monkey #19 did not appear to be sleepy, inactive or have heavy eyes and seemed to react similarly to all test compounds. She seems to be very comfortable in the chair, and when there were no distractions she tended to close her eyes and relax.

The dosing with bromonidine-linoleic acid complex appears to cause more sedation in the monkeys than dosing with saline. In general when the monkeys were dosed with saline, they were quiet and easy to handle for all readings. However, dosing with bromonidine tartrate causes more sedation than dosing with bromonidine-linoleic acid. When the monkeys were dosed with bromonidine tartrate, on average they became

sleepy and inactive with heavy eyes. This observation was seen usually at the 2-hour time point and most of the animals remained this way through the end of observations.

Without wishing to limit the invention to any mechanism or theory of operation, it is believed that one of the reasons that bromonidine-linoleic acid complex causes less sedation than bromonidine tartrate is that it partitions more in the lipid compartments. In other words, the bromonidine-linoleic acid complex is more trapped in the lipid compartments, and is not as available to circulate in the blood stream to eventually travel to the brain to cause sedation.

Example 3

Effects of bromonidine-linoleic acid ion pair complex (0.2%) on rabbit intraocular pressure

In this study, the animals were placed into three groups consisting of a mix of age, size and sex.

Group Number	Number of Animals Males	Number of Animals Females
1	4	4
2	4	4
3	4	4

One group of animals (both sexes) was used per screening study. The test compound (20μL of 0.2% bromonidine-linoleic acid ion pair complex) was administered to the surface of the cornea using an automatic pipette or an appropriate device.